Case report

Child Kidney Dis 2016;20:97-100
DOI: https://doi.org/10.3339/jkspn.2016.20.2.97

ISSN 2384-0242 (print)
ISSN 2384-0250 (online)

Two Cases of Toxic Epidermal Necrolysis Associated with Deflazacort Therapy in Nephrotic Syndrome: Successfully Treated with Cyclosporine A

Myung Hee Lim, M.D.
Hee Jung Bae, M.D.
Sun Young Park, M.D.
Sae Yoon Kim, M.D.
Yong Hoon Park, M.D.

Department of Pediatrics, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, Korea

Corresponding author: Yong Hoon Park, M.D.
Department of Pediatrics, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-053-620-3532
Fax: +82-053-629-2252
E-mail: yhpark@ynu.ac.kr

Received: 13 September 2016
Revised: 13 September 2016
Accepted: 10 October 2016

Toxic epidermal necrolysis (TEN) is a rare, acute, serious, and potentially fatal skin disease, in which cell death causes the epidermis to separate from the dermis. It is thought to be a hypersensitivity complex that affects the skin and mucous membranes, and is caused by certain medications, infections, genetic factors, underlying immunologic disease, or more rarely, cancers. We report two cases of TEN associated with deflazacort (DFZ), a derivative of prednisolone, used in the first episode of nephrotic syndrome (NS). The skin eruption appeared on the 4th and 5th weeks after DFZ administration, while NS was in remission. The widespread lesions were managed by intensive supportive treatment, discontinuation of DFZ, and oral administration of cyclosporine. Both patients showed a rapid improvement in symptoms of TEN without any complications or relapse of NS.

Key words: Toxic epidermal necrolysis, Deflazaocrt, Cyclosporine, Nephrotic syndrome

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are life-threatening mucocutaneous diseases with various clinical features from extensive epidermal detachment to severe systemic symptoms. TEN is a rare potentially fatal disease characterized by separation of the dermal-epidermal junction, necrosis, and destruction of the entire epidermal skin layer[1]. Drugs are the leading trigger of TEN in both adults and children.

TEN associated with DFZ therapy in NS has been reported in a few cases; Kim et al. reported a case of TEN in a 14-year-old boy caused by DFZ with enalapril given as treatment for NS; Lee et al. reported two cases of TEN associated with DFZ[2,3].

DFZ has been widely used instead of prednisone and prednisolone for managing NS because of its equivalent anti-inflammatory efficacy to prednisolone, and fewer side effects, such as less severe adverse effects on bone, less negative impact on growth rate in children, smaller effect on glucose metabolism, and growth retardation and with fewer gastrointestinal side effects[4]. TEN occurred in 3 out of 92 pediatric nephrotic syndrome patients who were administered DFZ in Yeungnam University Hospital between 2000 and 2016.

We report two cases of DFZ-induced TEN, where oral cyclosporine (CSA) was used early in the course of the disease and improved its progression without any complications.

Case reports

1. Case 1

A 12-year-old boy was admitted with multiple miliary to rice grain-sized erythematous crusted maculopapules and vesicles on his face, trunk, and both extremities, including both the palm and sole. There were also several erosive patches on his soft palate and buccal mucosa. About 5 weeks prior to this episode, he showed clinical features of minimal change NS. Remission was achieved within 2 weeks with DFZ at a dose of 72 mg per day. DFZ was given continuously to mange the first episode of NS according to KDIGO guideline.

His skin eruption begun to develop at on 32nd day of medication. He did not receive any other medications and had no previously known drug allergies. Laboratory findings were within the normal reference ranges: serum protein/albumin 6.08/4.26 g/day, serum blood urea nitrogen/creatinine 14.78/1.15 mg/dL, spot urine protein/creatinine ratio 0.15, white blood cells 15080/μL, hemoglobin 15.4 g/dL, platelets 221,000/μL. Normal vital signs were observed. There was no corneal involvement seen on opthalmological examination. Extensive wound care was performed, in which the detached skin was left in place to act like a biologic dressing. Appropriate fluid and electrolytes management were also provided. Although the skin lesions spread to the whole body within 3 days, it had regressed and begun to re-epithelialize after the administration of CSA (72 mg/day). After 1 week of treatment with CSA, the patient showed a rapid improvement in symptoms without complication and was subsequently discharged following a total of 17 days of hospitalization. Thus far, he has not experienced any repeated skin involvement despite administration of prednisolone to manage episodes of relapsed NS.

2. Case 2

A 12-year-old girl was admitted with multiple miliary to rice grain sized erythematous vesicles and papules on whole body with pain and itching. About 7 weeks before this episode, she showed clinical features of minimal change NS. She achieved remission with DFZ at a dose of 72 mg per day, and had continuously taken DFZ to manage her first episode of NS. During tapering of the medication dose (24 mg/day), her skin lesions were developed on the 8th day. Her skin lesions had begun development 5 days prior to admission, but had initially been diagnosed as chickenpox in a primary care clinic. She did not receive any other medications and had no previously known drug allergies. Laboratory findings were all in the normal reference range: serum protein/albumin 6.84/4.74 g/day, serum blood urea nigrogen/creatinine 8.77/0.64 mg/dL, spot urine protein/creatinine ratio 0.13, white blood cells 11,260/μL, hemoglobin 15.1 g/dL, and platelets 215,000/μL. On physical examination, she presented bilateral conjunctival injection without corneal involvement. DFZ was discontinued and changed to oral CSA 150mg per day immediately. The patient showed rapid regression of her skin symptoms and she was discharged 15 days after admission to the hospital without any complications.

Discussion

TEN, also known as Lyell's syndrome after first being suggested in 1956 by Lyell, is a mucocutaneous disease that can be life-threatening[5]. It is diagnosed when epidermal detachment involves more than 30% of the body surface area[6]. SJS is a variant of the same disease that involves less than 10% of body surface area[6]. They are thought to be a hypersensitivity complex that affects the skin and the mucous membranes and are caused by certain medications, infections, genetic factors, underlying immunologic disease, or cancers[6].

Although the exact mechanism of TEN associated with DFZ therapy is not known, Roujeau et al.[7] reported that exposure to corticosteroids significantly increased the risk of TEN. It is suggested that drug-induced TEN occurs due to the apoptosis of epithelial cells and a cascade of inflammatory reactions mediated by tumor necrosis factor and interferon-γ[8].

Despite the severity of the disease, there is no gold standard management for TEN. Prompt withdrawal of the offending drug, intensive care and monitoring of vital signs,

prevention of corneal involvement, and fluid management are all recommended[9]. The most commonly used treatments are immunoglobulin-G (IVIG), which contains anti-FasL antibodies and as a result may halt further epidermal necrosis and hasten re-epithelialization and controversial high-dose methylprednisolone therapy[9]. They are known to inhibit the development of skin lesions and reduce disease duration, and are attributed to improved survival rates. Second-line drugs include CSA, infliximab, and plasmapheresis[9].

Some retrospective studies show that treatment with IVIg resulted in a more rapid cessation of epidermal detachment and a survival rate of 88% of patients with TEN[10]. In 2006 a retrospective study found that the use of IVIG at a total dose of 2.8 g/kg/daily in 23 patients resulted in a marked difference in mortality compared with eight patients who received supportive therapy alone. The mortality rate was 26% in the patient group receiving IVIG and 75% in the group receiving supportive care alone[10].

Moreover, anti-tumor necrosis factor (TNF) therapy, such as infliximab and etanercept, has shown to be beneficial in a small number of case reports, although their benefit is not clear and further studies are needed[10]. Administration of N-acetyl cysteine is also known to enhance the detoxifying capacity of abnormal inherent metabolic pathways in TEN patients[10].

DFZ, a derivative of prednisolone is usually administered in children during the first episode of NS because of the presence of fewer side effects (e.g., growth retardation, osteoporosis, Cushing syndrome, etc.) than other corticosteroids[11]. Even though it has beneficial effects, DFZ can sometimes cause TEN. For example, Lee et al. reported two cases of TEN associated with DFZ therapy for NS, which were treated with IVIG[3]. Kim et al. reported a patient with NS developing TEN after DFZ medication. In this case, they used full-dose intravenous dexamethasone for TEN but the patient showed psychotic symptoms, so they tapered the steroid use and initiated IVIG[12].

It is known that the epidermal detachment of SJS/TEN is induced by the necrosis of keratinocytes following apoptosis[9]. CD 8+ T-lymphocytes, responsible for apoptosis, maturate to cytotoxic T-lymphocytes when activated by an adverse drug interaction [9]. CSA, an immunosuppressant, inhibits the cascades of immune responses mediated by T-lymphocytes and inflammatory mediators, and interferes with cell apoptosis that usually lead to the progression to SJS/TEN[9]. CSA has been shown to decrease the duration of active disease with a rapid re-epithelialization rate[13]. As modification of the doses and duration of treatment can reduce the risk of side effects, we successfully treated two patients with CSA at a dose of 3 mg/kg per day (daily maximum 150 mg). In terms of infection risk (corticosteroid pulse therapy) and cost-effectiveness (IVIG is expensive in Korea), CSA has its own benefits.

This is the first report using CSA to treat TEN associated with DFZ in a pediatric NS patient.

Even if this report is anecdotal, TEN associated sith DFZ was treated with oral administration of CSA, successfully reducing the duration of hospitalization and mortality rate and lowering medical expenses, with no notable complications.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child 2013;98: 998-1003.
2. Kim DW, Jung DE, Koo JW. Steroid and enalapril therapy-possible cause of toxic epidermal necrolysis. Korean J Pediatr 2006;49: 332-6.
3. Lee EC. Toxic epidermal necrolysis associated with deflazacort therapy with nephrotic syndrome. Kidney Res Clin Pract 2014;33: 222-5.
4. Wood ML, Gray RES, Kanis JA, Harrington CI. Deflazacort-a safer systemic steroid for the treatment of chronic dermatoses. Br J Dermatol 1985;113(s 29):34-5.
5. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.
6. Aihara Y, Ito R, Ito S, Aihara M, Yokota S. Toxic epidermal necrolysis in a child successfully treated with cyclosporine A and methylprednisolone. Pediatr Int 2007;49:659-62.
7. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.

8. Araki Y, Sotozono C, Inatomi T, Ueta M, Yokoi N, Ueda E, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. Am J Ophthalmol 2009;147:1004-11.
9. Hinc-Kasprzyk J, Polak-Krzeminska A, Ozog-Zabolska I. Toxic epidermal necrolysis. Anaesthesiol Intensive Ther 2015;47:257-62.
10. Fernando SL. The management of toxic epidermal necrolysis. Australas J Dermatol 2012;53:165-71.
11. Jat KR, Khairwa A. Deflazacort in comparison to other steroids of nephrotic syndrome. Indian J Nephrol 2012;22:239-45.
12. Kim SY, Lee JM, Park YH. A case of steroid-induced psychosis in a child having nephrotic syndrome with toxic epidermal necrolysis. Korean J Pediatr 2010;53:437-41.
13. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporine A. Trauma 2000;48:473-8.